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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,865	08/06/2003	Andrew David Carlson	X-11408C	8787

25885 7590 08/29/2005

ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,865	CARLSON ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15 and 17-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15 and 17-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDD

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on August 11, 2005 has been entered.

No claims have been amended. No claims have been canceled. Claims 29-31 have been added. Accordingly, claims 13-15 and 17-31 are pending and are examined on the merits herewith.

The text of those sections of Title 35, U.S. code, not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15 and 17-31 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements, which are absent from claim 13, are, firstly, that a reconstituted or redissolved or rehydrated lyophilized

formulation is administered to a patient to treat one of the diseases listed in the preamble. This reconstituted or redissolved or rehydrated preparation is administered by injection; the dry powder of a lyophilized preparation is not administered (because it cannot be injected or infused over time, and the specification does not disclose methods in which a dry powder may be used, such as oral or pulmonary administration). The specification describes on pages 8 and 9 the buffer solutions that may be added to the activated protein C (aPC) solution before lyophilization. The presence of a buffer indicates that the preparation is intended to be rehydrated before use.

Secondly, the claims do not recite the essential feature that the preparation that is administered contains aPC, a bulking agent and a salt (potassium chloride or sodium chloride, preferably sodium chloride) in a ratio of 1:5-7:7-8. See p. 9, line 7, to p. 10, line 20, of the specification. Applicants note that "ionic strength is a critical variable to ensure solution stability" and that the "ratio of aPC:salt:bulking agent (w:w:w) is an important factor in a formulation suitable for the freeze drying process. The ratio varies depending on the concentration of aPC, salt selection and concentration and bulking agent selection and concentration." A formulation matrix, Table 1, lists a few combinations of concentrations of aPC, sucrose (as the bulking agent) and NaCl that are and are not suitable for stable lyophilized preparations. It is clear that at least a three-component preparation- of aPC, bulking agent and salt- is required in the claimed method. Appropriate correction is requested.

Claim Rejections - 35 USC § 103

Claims 13-15 and 17-28 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Hirahara (US 5,084,273) in view of Mochida Pharmaceutical Co. Ltd. (JP 08-301786, see enclosed English machine translation). This rejection was discussed in two previous Office actions. Claims 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirahara (US 5,084,273) in view of Mochida Pharmaceutical Co. Ltd. (JP 08-301786, see enclosed English machine translation) and Lehninger (Principles of Biochemistry, Worth Publishers, Inc. New York, 1982, pp. 83 and 85).

Further, with regard to the essential elements discussed above that are missing from the claims, Hirahara discloses a method of treating blood coagulation in patients by administering a rehydrated lyophilized preparation of aPC. The preparation contains aPC, bulking agent (mannitol) and sodium chloride in a ratio of 1:67:60 (1.5 mg of aPC, 100 mg of mannitol and 90 mg of NaCl). Mochida discloses a lyophilized preparation of aPC, mannitol and sodium chloride that may be rehydrated to produce a therapeutic agent in which the ratio of these components is 1:2.5:8.2 (10 mg of aPC, 25 mg of mannitol and 81.8 mg of NaCl). Mochida discloses that this therapeutic agent may be used to treat bone absorption diseases. But, Mochida also discloses that aPC may be administered as an anticoagulant and that receptors for aPC are present on vascular endothelial cells (see paragraph 5). It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the preparation of Mochida for the uses disclosed by Hirahara and Mochida, that is, to treat blood clots in a patient,

because Mochida discloses a formulation according to which aPC may be lyophilized and reconstituted in an active and stable state.

As noted above, the ratio of aPC:bulking agent:NaCl in the preparation of Mochida is 1:2.5:8.2. This is not substantially different than Applicants' partially claimed and preferred ratio of 1:5-7:7-8. As previously discussed, Applicants' preferred ratio is not associated with any particular result or unexpected effect. Although Applicants' preferred ratio yields a stable product, the preparations of Hirahara and Mochida are also formulated to yield stable products with respect to aPC. Thus, different formulations of aPC containing a bulking agent and NaCl may confer stability, particularly those that are similar to the preparations of Hirahara or Mochida.

Regarding claims 29-30, Mochida discloses that the buffering agent in the preparation is sodium phosphate, as in Applicants' claimed method. Sodium phosphate buffers (a mixture of sodium dihydrogen phosphate and disodium hydrogen phosphate) are used for solutions where the desired pH is close to neutral or in the range of 6.1 to 7.7 (see Lehninger, enclosed).

Regarding claim 31, the cited references do not specifically disclose the amount or percentage of aPC degradation products in the aPC preparation. Nevertheless, as discussed above, the preparations in the cited art, especially that of Mochida, are formulated for stability. Because the composition of Mochida is very similar to that of Applicants, absent evidence to the contrary, one of ordinary skill in the art would reasonably expect the preparation of Mochida to have the same properties as that of Applicants, i.e., a low level of degradation products.

Therefore, a holding of obviousness is required.

All of Applicants' arguments have been considered, but they are not persuasive of error. Firstly, Applicants state that a case for obviousness cannot be made because motivation to combine the references was not provided, the proposed modification of the reference does not have a reasonable expectation of success, and the prior art does not teach all the limitations of the claims. In reply, Applicants provide no evidence or support for their statement. Motivation to combine the references was provided in the previous Office actions and is as mentioned above, i.e., that both Hirahara and Mochida disclose therapeutic aPC preparations for use as anticoagulants. The ratio of aPC to mannitol (as a bulking agent) differs between the two, but both are effective preparations that can be lyophilized. One of ordinary skill in the art would have been motivated to substitute one preparation for another, i.e., the preparation of Mochida in the method of Hirahara, because both preparations have the same active ingredient and achieve the same result. Regarding teaching all the claim limitations, the rejection in the previous Office actions is the combination of the teachings of Hirahara and Mochida, which teach that therapeutically effective preparations of aPC may have different ratios of aPC to bulking agent. Hirahara teaches 1:67 and Mochida teaches 1:2.5. The ratio of Mochida differs only two-fold from Applicants' ratio. Because Applicants disclose no special properties resulting from a ratio of 1:5-7 compared to other ratios, one of ordinary skill in the art would expect a composition with a ratio of 1:2.5 to behave similarly to a composition with a ratio of 1:5. As noted previously, this is a result-

effective parameter that would have been easily adjusted as needed by one of ordinary skill in the art.

Secondly, Applicants note that Hirahara does not disclose a wide range of aPC concentrations in his preparations, but they note that Hirahara discloses concentrations of 2-20 μg/ml in the therapeutic compositions and an amount of total protein per dose in the range of 5 mg to 1 g for a 60 kg adult. These appear to be fairly wide ranges. Applicants note that the ratio of aPC to mannitol does not vary in the lyophilized preparation, and they discuss how a dose is different from a preparation. But, the calculations on p. 7 of Applicants' response are in error because they are based on using 5 mg - 1 g of aPC for a 60 kg adult. Hirahara states that these are the amounts of total protein in the preparation, not the amounts of aPC.

Claims 18 and 19 are the only claims that recite a dosage, 0.01-0.05 mg/kg/hr. At this rate, a 60 kg adult would receive 0.6-3.0 mg/hr. In Hirahara, the preparation of Example 1 contains 0.15 mg of aPC per ml. An effective dosage contains 2-20 μg/ml. Thus, the preparation is to be diluted at a ratio of 1:7.5 to 1:75 for use. 100 ml of a diluted preparation would contain 0.2 to 2.0 mg of aPC. If this 100 ml were infused into a patient over an hour, the dosing regimes of Hirahara and Applicants' claimed method would be comparable. Hirahara discloses only the total amount of protein to be given to a subject, based on his weight, and does not specifically indicate the length of time over which the therapeutic agent is to be administered. But instant claim 18 recites that the aPC preparation may be administered for 1-48 hours. Thus, the length of time of aPC administration does not appear to be a critical or specific number.

Thirdly, Applicants state that Mochida teaches away from the ratio of aPC to bulking agent as a result-effective parameter because the reference discloses two examples in which this ratio is different. The ratios are 1:2.5 and 1:0.5. These examples teach that the preparation disclosed in each one provides an effective amount of aPC. These examples do not teach away from manipulation of the ratio of aPC to bulking agent.

Fourthly, Applicants note that they are the first to disclose a formulation that reduces the autodegradation of aPC and that this formulation would not be obvious from reading the cited references. But, apart from new claim 31, the autodegradation of aPC is not a limitation recited in the claims. As mentioned above, Applicants' formulation of aPC, bulking agent and NaCl does not differ appreciably from that of Mochida. Additionally, Applicants have provided data showing the effect of several concentrations of NaCl in solutions that contain a fixed amount of aPC and bulking agent (Table 1). These data show that, for stability, sufficient NaCl must be present so that crystals form during lyophilization. No data, however, is presented to show the effect of varying the concentration of the bulking agent. Consequently, Applicants have not shown that varying the amount of bulking agent while keeping the amounts of aPC and NaCl constant has any effect on aPC stability or aPC autodegradation. Furthermore, the claimed method is a method of treating a patient, not a method of manufacturing a drug. In the claimed method, a reconstituted form of a lyophilized preparation is injected into or infused into a patient, most likely intravenously. Once inside the patient's circulatory system, the components of the aqueous solution diffuse away from each other and

interact with the contents of the blood vessels. The claims do not recite that the bulking agent is chemically bound to the aPC. Thus, any effect of the bulking agent on the aPC diminishes over time as the aPC circulates through the patient's body. In the lyophilized or reconstituted aPC preparation, a particular ratio of aPC to bulking agent may affect stability. But this ratio would not play a role in a method of treatment in which the components of the aPC preparation are dissolved and diffuse through a patient's body.

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1653

rk/2005-08-22

ROBERT A. WAX
PRIMARY EXAMINER